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* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS 4	FEB 21	STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results
NEWS 5	FEB 22	The IPC thesaurus added to additional patent databases on STN
NEWS 6	FEB 22	Updates in EPFULL; IPC 8 enhancements added
NEWS 7	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS 8	MAR 03	Updates in PATDPA; addition of IPC 8 data without attributes
NEWS 9	MAR 22	EMBASE is now updated on a daily basis
NEWS 10	APR 03	New IPC 8 fields and IPC thesaurus added to PATDPAFULL
NEWS 11	APR 03	Bibliographic data updates resume; new IPC 8 fields and IPC thesaurus added in PCTFULL
NEWS 12	APR 04	STN AnaVist $500 visualization usage credit offered
NEWS 13	APR 12	LINSPEC, learning database for INSPEC, reloaded and enhanced
NEWS 14	APR 12	Improved structure highlighting in FQHIT and QHIT display in MARPAT
NEWS 15	APR 12	Derwent World Patents Index to be reloaded and enhanced during second quarter; strategies may be affected
NEWS 16	MAY 10	CA/CAplus enhanced with 1900-1906 U.S. patent records
NEWS 17	MAY 11	KOREAPAT updates resume
NEWS 18	MAY 19	Derwent World Patents Index to be reloaded and enhanced
NEWS 19	MAY 30	IPC 8 Rolled-up Core codes added to CA/CAplus and USPATFULL/USPAT2
NEWS 20	MAY 30	The F-Term thesaurus is now available in CA/CAplus
NEWS 21	JUN 02	The first reclassification of IPC codes now complete in INPADOC
NEWS EXPRESS		FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005. V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT http://download.cas.org/express/v8.0-Discover/
NEWS HOURS		STN Operating Hours Plus Help Desk Availability
NEWS LOGIN		Welcome Banner and News Items
NEWS IPC8		For general information regarding STN implementation of IPC 8
NEWS X25		X.25 communication option no longer available after June 2006

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:36:36 ON 13 JUN 2006

=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'REGISTRY' ENTERED AT 14:36:47 ON 13 JUN 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file
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STRUCTURE FILE UPDATES:   12 JUN 2006  HIGHEST RN 887497-01-0
DICTIONARY FILE UPDATES:  12 JUN 2006  HIGHEST RN 887497-01-0

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

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  conducting SmartSELECT searches.

*********************************************************************
*                                                                   *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                   *
*********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> E "RM2"/CN 25
E1            1     RM-ACID/CN
E2            1     RM189/CN
E3            0 --> RM2/CN
E4            1     RM38/CN
E5            1     RM60 HOMOPOLYMER/CN
E6            1     RM7/CN
E7            1     RM711/CN
E8            1     RM715/CN
E9            1     RM721/CN
E10           1     RM723/CN
E11           1     RM80/CN
E12           1     RM801FW/CN
E13           2     RMA 1/CN
E14           1     RMA 1 (FLUX)/CN
E15           1     RMA 1 (RUBBER)/CN
E16           1     RMA 101/CN
E17           1     RMA 150M/CN
```

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E18             1      RMA 1X/CN
E19             1      RMA 2/CN
E20             1      RMA 300M/CN
E21             1      RMA 325/CN
E22             1      RMA 390DH3/CN
E23             1      RMA 4/CN
E24             1      RMA 400/CN
E25             1      RMA 450M/CN

=> E "RM-2"/CN 25
E1              1      RM LUTE/CN
E2              1      RM PROTEIN (BACILLUS THURINGIENSIS ENTOMOCIDUS STRAIN LBIT-113
PLASMID PUIBI-1)/CN
E3              0 --> RM-2/CN
E4              1      RM-ACID/CN
E5              1      RM189/CN
E6              1      RM38/CN
E7              1      RM60 HOMOPOLYMER/CN
E8              1      RM7/CN
E9              1      RM711/CN
E10             1      RM715/CN
E11             1      RM721/CN
E12             1      RM723/CN
E13             1      RM80/CN
E14             1      RM801FW/CN
E15             2      RMA 1/CN
E16             1      RMA 1 (FLUX)/CN
E17             1      RMA 1 (RUBBER)/CN
E18             1      RMA 101/CN
E19             1      RMA 150M/CN
E20             1      RMA 1X/CN
E21             1      RMA 2/CN
E22             1      RMA 300M/CN
E23             1      RMA 325/CN
E24             1      RMA 390DH3/CN
E25             1      RMA 4/CN

=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.44       0.65

FILE 'CAPLUS' ENTERED AT 14:37:36 ON 13 JUN 2006
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COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 13 Jun 2006  VOL 144 ISS 25
FILE LAST UPDATED: 12 Jun 2006  (20060612/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:
```

http://www.cas.org/infopolicy.html

=> s us 20050221397/pn
L1 1 US 20050221397/PN
(US2005221397/PN)

=> sel rn
E1 THROUGH E1 ASSIGNED

=> file reg
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 2.49 3.14

FILE 'REGISTRY' ENTERED AT 14:37:55 ON 13 JUN 2006
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Property values tagged with IC are from the ZIC/VINITI data file
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STRUCTURE FILE UPDATES: 12 JUN 2006 HIGHEST RN 887497-01-0
DICTIONARY FILE UPDATES: 12 JUN 2006 HIGHEST RN 887497-01-0

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TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Structure search iteration limits have been increased. See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> s e1
L2 1 850223-38-0/BI
(850223-38-0/RN)

=> d ibib
'IBIB' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'

The following are valid formats:

Substance information can be displayed by requesting individual
fields or predefined formats. The predefined substance formats
are: (RN = CAS Registry Number)

REG   - RN
SAM   - Index Name, MF, and structure - no RN
FIDE   - All substance data, except sequence data
IDE   - FIDE, but only 50 names
SQIDE - IDE, plus sequence data
SQIDE3 - Same as SQIDE, but 3-letter amino acid codes are used
SQD   - Protein sequence data, includes RN
SQD3   - Same as SQD, but 3-letter amino acid codes are used
SQN   - Protein sequence name information, includes RN

CALC   - Table of calculated properties
EPROP - Table of experimental properties
PROP   - EPROP and CALC

Any CA File format may be combined with any substance format to
obtain CA references citing the substance. The substance formats
must be cited first. The CA File predefined formats are:

ABS -- Abstract
APPS -- Application and Priority Information
BIB -- CA Accession Number, plus Bibliographic Data
CAN -- CA Accession Number
CBIB -- CA Accession Number, plus Bibliographic Data (compressed)
IND -- Index Data
IPC -- International Patent Classification
PATS -- PI, SO
STD -- BIB, IPC, and NCL

IABS -- ABS, indented, with text labels
IBIB -- BIB, indented, with text labels
ISTD -- STD format, indented

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

The ALL format gives FIDE BIB ABS IND RE, plus sequence data when
it is available.
The MAX format is the same as ALL.
The IALL format is the same as ALL with BIB ABS and IND indented,
with text labels.

For additional information, please consult the following help
messages:

HELP DFIELDS -- To see a complete list of individual display fields.
HELP FORMATS -- To see detailed descriptions of the predefined formats.
ENTER DISPLAY FORMAT (IDE):end

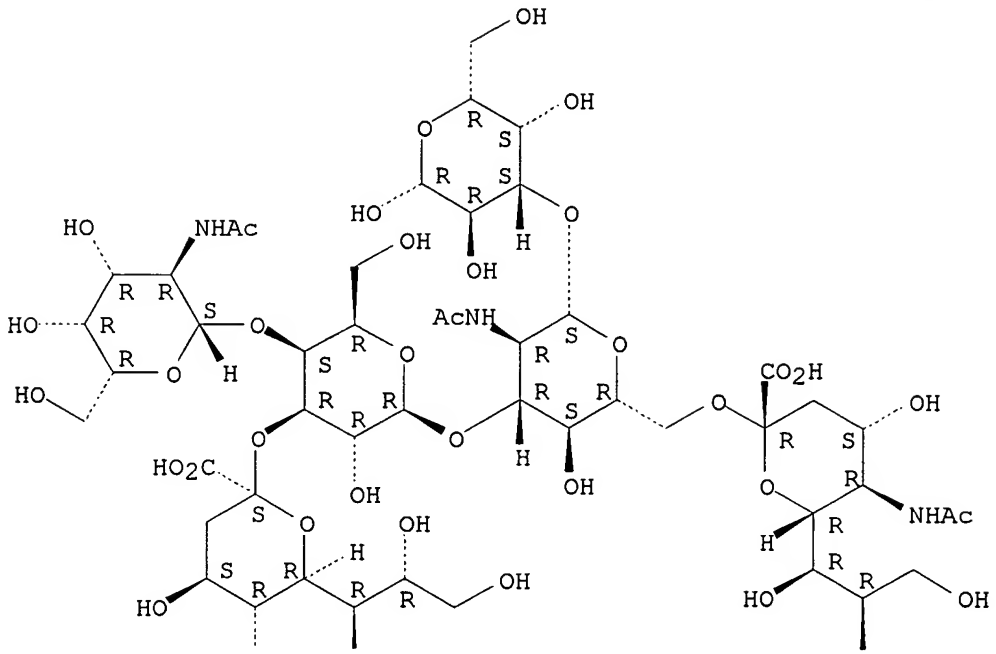
=> d 1

L2   ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN
RN   850223-38-0 REGISTRY
ED   Entered STN: 11 May 2005
CN   β-D-Galactopyranose, O-2-(acetylamino)-2-deoxy-β-D-
     galactopyranosyl-(1→4)-O-[N-acetyl-α-neuraminosyl-
     (2→3)]-O-β-D-galactopyranosyl-(1→3)-O-[N-acetyl-α-
     neuraminosyl-(2→6)]-O-2-(acetylamino)-2-deoxy-β-D-
     glucopyranosyl-(1→3)- (9CI) (CA INDEX NAME)
FS   STEREOSEARCH
MF   C50 H82 N4 O37
SR   CA

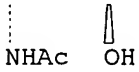
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.34	5.48

FILE 'CAPLUS' ENTERED AT 14:38:27 ON 13 JUN 2006
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FILE LAST UPDATED: 12 Jun 2006 (20060612/ED)

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=> d his

     (FILE 'HOME' ENTERED AT 14:36:36 ON 13 JUN 2006)

     FILE 'REGISTRY' ENTERED AT 14:36:47 ON 13 JUN 2006
               E "RM2"/CN 25
               E "RM-2"/CN 25

     FILE 'CAPLUS' ENTERED AT 14:37:36 ON 13 JUN 2006
L1   1 S US 20050221397/PN
               SEL RN

     FILE 'REGISTRY' ENTERED AT 14:37:55 ON 13 JUN 2006
L2   1 S E1

     FILE 'CAPLUS' ENTERED AT 14:38:27 ON 13 JUN 2006

=> s l2
L3   2 L2

=> d ibib 1-2

L3   ANSWER 1 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1078089 CAPLUS
DOCUMENT NUMBER: 143:344596
TITLE: Rm2 antigen (beta1,4-galnac-disialyl-lc4) as prostate
                          cancer-associated antigen
INVENTOR(S):   Saito, Seiichi
PATENT ASSIGNEE(S):   Northern Advancement Center for Science & Technology,
                          S. Korea
SOURCE: U.S. Pat. Appl. Publ., 13 pp.
                          CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

     PATENT NO.   KIND   DATE   APPLICATION NO.   DATE
     ---------------   ----   --------   --------------------   --------
     US 2005221397   A1   20051006   US 2004-812357   20040330
     WO 2005098434   A2   20051020   WO 2005-US10221   20050325
         W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM,
             SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
             RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:   US 2004-812357   A 20040330

```
L3   ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2005:373084  CAPLUS
DOCUMENT NUMBER:          142:408646
TITLE:                    RM2 antigen (β1,4-GalNAc-disialyl-Lc4) as a new
                          marker for prostate cancer
AUTHOR(S):                Saito, Seiichi; Egawa, Shin; Endoh, Mareyuki; Ueno,
                          Seiji; Ito, Akihiro; Numahata, Kenji; Satoh, Makoto;
                          Kuwao, Sadahito; Baba, Shiro; Hakomori, Senitiroh;
                          Arai, Yoichi
CORPORATE SOURCE:         Department of Urology, Tohoku University Graduate
                          School of Medicine, Sendai, Japan
SOURCE:                   International Journal of Cancer (2005), 115(1),
                          105-113
                          CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER:                Wiley-Liss, Inc.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          33    THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> file pctfull
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     3.20       8.68

FILE 'PCTFULL' ENTERED AT 14:39:42 ON 13 JUN 2006
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FILE LAST UPDATED:         13 JUN 2006      <20060613/UP>
MOST RECENT UPDATE WEEK:       200623        <200623/EW>
FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

>>> NEW IPC8 DATA AND FUNCTIONALITY NOW AVAILABLE IN THIS FILE.
    SEE
    http://www.stn-international.de/stndatabases/details/ipc-reform.html >>>

>>> FOR CHANGES IN PCTFULL PLEASE SEE HELP CHANGE
    (last updated April 10, 2006) <<<

=> s RM2
L4          397 RM2

=> s antibod?
L5        88553 ANTIBOD?

=> s l5 and l4
L6           95 L5 AND L4

=> s cancer? or tumor? or neoplas?
          78950 CANCER?
          65926 TUMOR?
          22900 NEOPLAS?
L7        98312 CANCER? OR TUMOR? OR NEOPLAS?

=> s l6 and l7
L8           67 L6 AND L7

=> s prostate and l8
          24530 PROSTATE
            421 PROSTATES
```

```
         24544 PROSTATE
                (PROSTATE OR PROSTATES)
L9          23 PROSTATE AND L8

=> s l9 not py>2002
        408573 PY>2002
L10          8 L9 NOT PY>2002

=> d ibib 1-8

L10    ANSWER 1 OF 8     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:        2002056022 PCTFULL  ED 20020725  EW 200229
TITLE (ENGLISH):         DIAGNOSTIC TUMOR MARKERS, DRUG SCREENING FOR
                         TUMORIGENESIS INHIBITION, AND COMPOSITIONS AND
                         METHODS FOR TREATMENT OF CANCER
TITLE (FRENCH):          MARQUEURS TUMORAUX DE DIAGNOSTIC, ANALYSE DE
                         MEDICAMENTS POUR L'INHIBITION DE LA
                         TUMORIGENESE, ET COMPOSITIONS ET PROCEDES POUR
                         LE TRAITEMENT DU CANCER
INVENTOR(S):             BAMDAD, Cynthia, C., 142 Church Street, Newton, MA
                         02458, US;
                         BAMDAD, R., Shoshana, 142 Church Street, Newton, MA
                         02458, US
PATENT ASSIGNEE(S):      MINERVA BIOTECHNOLOGIES CORPORATION, 142 Church Street,
                         Newton, MA 02458, US [US, US]
AGENT:                   POMIANEK, Michael, J.$, Wolf, Greenfield & Sacks, P.C.,
                         600 Atlantic Avenue, Boston, MA 02210$, US
LANGUAGE OF FILING:      English
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER              KIND     DATE
                         ---------------------------------
                         WO 2002056022         A2 20020718
DESIGNATED STATES
       W:                AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR
                         CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID
                         IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD
                         MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI
                         SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
       RW (ARIPO):       GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
       RW (EAPO):        AM AZ BY KG KZ MD RU TJ TM
       RW (EPO):         AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
                         TR
       RW (OAPI):        BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.:       WO 2001-US44782       A  20011127
PRIORITY INFO.:          US 2000-60/253,361       20001127
                         US 2000-60/255,370       20001213
                         US 2000-60/256,027       20001215
                         US 2000-60/258,157       20001222
                         US 2001-60/259,615       20010103
                         US 2001-60/260,186       20010105
                         US 2001-60/266,169       20010202
                         US 2001-60/266,929       20010206
                         US 2001-60/278,093       20010323
                         US 2001-60/289,444       20010507
                         US 2001-60/294,887       20010531
                         US 2001-60/298,272       20010614

L10    ANSWER 2 OF 8     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:        2001042786 PCTFULL  ED 20020827
TITLE (ENGLISH):         SYSTEM FOR CELL BASED SCREENING : CELL SPREADING
TITLE (FRENCH):          SYSTEME DE CRIBLAGE A BASE DE CELLULES
INVENTOR(S):             SAMMAK, Paul;
```

DUENSING, Thomas, D.;
RUBIN, Richard

PATENT ASSIGNEE(S): CELLOMICS, INC.;
SAMMAK, Paul;
DUENSING, Thomas, D.;
RUBIN, Richard

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001042786	A2	20010614

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2000-US33308 A 20001208
PRIORITY INFO.: US 1999-60/170,087 19991209

L10 ANSWER 3 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2001000247 PCTFULL ED 20020828
TITLE (ENGLISH): PEPTIDE-LIPID CONJUGATES, LIPOSOMES AND LIPOSOMAL DRUG DELIVERY
TITLE (FRENCH): CONJUGUES PEPTIDES-LIPIDES, LIPOSOMES ET APPORT DE MEDICAMENTS LIPOSOMIQUES
INVENTOR(S): MEERS, Paul;
PAK, Charles;
ALI, Shaukat;
JANOFF, Andrew;
FRANKLIN, J., Craig;
ERUKULLA, Ravi;
CABRAL-LILLY, Donna;
AHL, Patrick
PATENT ASSIGNEE(S): THE LIPOSOME COMPANY, INC.
DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001000247	A1	20010104

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2000-US16248 A 20000613
PRIORITY INFO.: US 1999-09/343,650 19990629

L10 ANSWER 4 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2000072686 PCTFULL ED 20020515
TITLE (ENGLISH): REGULATION OF SYSTEMIC IMMUNE RESPONSES UTILIZING CYTOKINES AND ANTIGENS
TITLE (FRENCH): REGULATION DE LA REPONSE IMMUNITAIRE SYSTEMIQUE A L'AIDE DE CYTOKINES ET D'ANTIGENES
INVENTOR(S): HARDY, Steve;
DRANOFF, GlennRP : NAKAMURA, Dean
PATENT ASSIGNEE(S): CELL GENESYS, INC.

LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000072686	A1	20001207

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2000-US15190 A 20000602
PRIORITY INFO.: US 1999-09/324,707 19990602

L10 ANSWER 5 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2000057899 PCTFULL ED 20020515
TITLE (ENGLISH): THROMBOSPONDIN-2 AND USES THEREOF
TITLE (FRENCH): LA THROMBOSPONDINE-2 ET SES UTILISATIONS
INVENTOR(S): DETMAR, Michael;
STREIT, Michael
PATENT ASSIGNEE(S): THE GENERAL HOSPITAL CORPORATION;
DETMAR, Michael;
STREIT, Michael
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000057899	A1	20001005

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2000-US7835 A 20000324
PRIORITY INFO.: US 1999-60/127,221 19990331

L10 ANSWER 6 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2000029433 PCTFULL ED 20020515
TITLE (ENGLISH): 12-25-KDA BACTERIAL PROTEINS AND THEIR 116-58 KDA POLYMERS FOR USE E.G. IN ANTI-TUMOR VACCINES
TITLE (FRENCH): PRODUIT
INVENTOR(S): KISLITCHKINE, Nikolay
PATENT ASSIGNEE(S): TOLIN AS;
JONES, Elizabeth, Louise;
KISLITCHKINE, Nikolay
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000029433	A2	20000525

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX

NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA
UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG ZW
AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR
GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW
ML MR NE SN TD TG

APPLICATION INFO.: WO 1999-GB3852 A 19991118
PRIORITY INFO.: RU 1998-98120511 19981118
GB 1999-9908663.9 19990415

L10 ANSWER 7 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1997033908 PCTFULL ED 20020514
TITLE (ENGLISH): LYTIC PEPTIDES
TITLE (FRENCH): PEPTIDES LYTIQUES
INVENTOR(S): RIVETT, Donald, Edward;
HUDSON, Peter, John;
WERKMEISTER, Jerome, Anthony
PATENT ASSIGNEE(S): COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION;
RIVETT, Donald, Edward;
HUDSON, Peter, John;
WERKMEISTER, Jerome, Anthony
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9733908	A1	19970918

DESIGNATED STATES
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE
ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS
LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG
SI SK TJ TM TR TT UA UG US UZ VN YU GH KE LS MW SD SZ
UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR
GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML
MR NE SN TD TG

APPLICATION INFO.: WO 1997-AU160 A 19970313
PRIORITY INFO.: AU 1996-PN 8614 19960313

L10 ANSWER 8 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1995019169 PCTFULL ED 20020514
TITLE (ENGLISH): TREATMENT OF PLATELET DERIVED GROWTH FACTOR RELATED DISORDERS SUCH AS CANCERS USING INHIBITORS OF PLATELET DERIVED GROWTH RECEPTOR
TITLE (FRENCH): TRAITEMENT DE TROUBLES LIES AU FACTEUR MITOGENIQUE PLAQUETTAIRE TELS QUE LES CANCER, UTILISANT DES INHIBITEURS DU RECEPTEUR DE FACTEUR MITOGENIQUE PLAQUETTAIRE
INVENTOR(S): HIRTH, Klaus, Peter;
SCHWARTZ, Donna, Pruess;
MANN, Elaina;
SHAWVER, Laura, Kay;
KERI, Gyorgy;
SZEKELY, Istvan;
BAJOR, Tamas;
HAIMICHAEL, Janis;
ORFI, Laszlo;
LEVITZKI, Alex;
GAZIT, Aviv;
ULLRICH, Axel;
LAMMERS, Reiner;
KABBINAVAR, Fairooz, F.;
SLAMON, Dennis, J.;
TANG, Cho, Peng
PATENT ASSIGNEE(S): SUGEN, INC.;

BIOSIGNAL LTD.;
YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY OF JERUSALEM;
MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V.;
REGENTS OF THE UNIVERSITY OF CALIFORNIA

LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9519169	A2	19950720

DESIGNATED STATES
W: AM AT AU BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU JP KE KG KP KR KZ LK LR LT LU LV MD MG MN MW MX NL NO NZ PL PT RO RU SD SE SI SK TJ TT UA UZ VN KE MW SD SZ AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1995-US363 A 19950106
PRIORITY INFO.: US 1994-8/179,570 19940107

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L10 ANSWER 1 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
TIEN DIAGNOSTIC TUMOR MARKERS, DRUG SCREENING FOR TUMORIGENESIS INHIBITION, AND COMPOSITIONS AND METHODS FOR TREATMENT OF CANCER
TIFR MARQUEURS TUMORAUX DE DIAGNOSTIC, ANALYSE DE MEDICAMENTS POUR L'INHIBITION DE LA TUMORIGENESE, ET COMPOSITIONS ET PROCEDES POUR LE TRAITEMENT DU CANCER
ABEN . . . a series of compositions, methods, kits, articles and species associated primarily with the diagnosis and/or treatment of cell proliferation, specifically cancer. Cell proliferation associated with aberrant expression of MUCI is particularly focused upon. Mechanisms associated with MUCI cell proliferation are discussed.
ABFR . . . de procedes, de trousses, d'articles et d'especes associes principalement au diagnostic et/ou au traitement de la proliferation cellulaire, notamment du cancer. L'invention concerne en particulier la proliferation cellulaire associee a l'expression aberrante de MUC1, ainsi que des mecanismes associes a la. . .

DETD DIAGNOSTIC TUMOR MARKERS, DRUG SCREENING FOR TUMORIGENESIS INHIBITION, AND COMPOSITIONS AND METHODS FOR TREATMENT OF CANCER
Related Applications
This non-provisional application claims the benefit under Title 35, U.S.C.

Field of the Invention
The invention relates to assays using shed cell surface receptor interchain binding
regions and cleavage products for cancer diagnosis, and for the evaluation of cancer
treatment and using the portion of the receptor that remains on the cell as a molecular
target for cancer therapeutics.
. . .
of the Invention
Many of the biomolecular interactions that promote turnorigenesis involve cell
surface proteins that mediate both intra- and intercellular signaling. Tumor markers are
proteins on the surface of a cell that are exclusively expressed,

over-expressed or show
an altered expression pattern as a result of transformation to a
neoplastic state. The
surface concentration of certain tumor markers has been
correlated to the progression of
cancer. For example, the interaction between the cell surface
receptor aVP3 and the cell
adhesion molecule vitronectin has been implicated in angiogenesis. . .

Integrins and cancer. Curr Opin Cell Biol, 1996, 8(5):
724-730; Vailhe B, Ronot X,
Tracqui P, Usson Y, Tracqui L: In vitro angiogenesis is. . .

Cell surface receptors, that have been linked to cancer, make
up an important
class of therapeutic targets. Many pharmaceutical companies are actively
involved in
screening drug libraries for compounds that bind to and block these cell
surface
receptors. For example, an important drug used to treat breast
cancer is Herceptin
(Pegram M, Lipton A, Hayes D, Webber B, Baselga J, Tripathy D, Baly D,
Baughman S,
Twaddell T, Glaspy J, Slamon D: Phase II study of receptor-enbanced
chemosensitivity
using recombinant humanized anti-p 1 8 5 Her2/neu monoclonal
antibody plus cisplatin, in
patients with Her2/neu-overexpressing metastatic breast cancer
refractory to
chemotherapy treatment, J Clin Oncol, 1998, 16(8): 2659-267 1). This
drug binds to and
blocks HER2/neu (Ross J, Fletcher J: review, The Her2/neu oncogene in
breast cancer.
. . .
for therapy. Stem Cells, 1998, 16(6): 413-
428) which is a cell surface receptor that is over-expressed on 30% of
breast tumors.
. . .
myeloma cells and is induced
by dexamethasone. Blood, 1999, 93(4): 1287-1298), is especially
interesting since it is
aberrantly expressed on many human tumors, including 80% of
breast tumors, and on a
significant percentage of prostate, lung, ovarian, colorectal
and perhaps brain, cancers.
. . .
epithelium, MUC I is clustered at, the apical border and is not
expressed over other portions of the cell. However, in tumor
cells, the receptor is
homogeneously over-expressed over the entire cell surface (Kufe D.,
Inghirami G., Abe
M., Hayes D, Justi-Wheeler H, Schlom J: Differential reactivity of a
novel monoclonal
antibody (DF3) with human malignant versus benign breast
tumors. Hybridoma, 1984, 3.

223-232), rather than just at the apical border. It is also known that
women with breast
cancer have elevated levels of shed MUC 1 receptor in their
blood stream. Extracellular
portions of the MUC I receptor are cleaved. . . least one enzyme, and
released into the blood stream. Levels of shed MUC I receptor in serum
are measured to
track breast cancer patients for recurrence. However, the

method is too variable and
insensitive to be used as a general diagnostic.

Until now, the mechanistic link between the MUC I receptor and tumorigenesis
has not been understood. Attempts to correlate the number of repeat units, which varies
from person to person, and susceptibility to cancer failed. Investigations of a possible
connection, between glycosylation of the MUCl receptor and cancer, produced
conflicting results. Importantly, until now, a fimctional figand(s) for the extracellular
portion of the MUC 1 receptor has not been identified.

Absent an understanding of the mechanism of the MUC I receptor, and how it
triggers tumorigenesis, it has not been possible to design or identify therapeutics'that
interfere with the disease-associated ftinction of this receptor. Indeed, currently there. . .

The present invention describes discoveries that elucidate critical aspects of the
mechanism by which WC I triggers cell proliferation and tumorigenesis. These
discoveries provide novel molecular targets for drug screening assays which the
inventors have used to identify compounds that inhibit the WC. . .
. . .
of the Invention
The present invention provides a variety of kits, methods, compositions, peptide
species and articles associated with cell proliferation, specifically cancer. The invention
involves primarily techniques and components for the diagnosis and treatment of cancer.

Another method of the invention involves treating a subject having cancer or
3o being at risk for developing cancer, the method comprises administering to the subject an
agent that reduces cleavage of a cell surface receptor.

Another method of the invention for treating a subject having cancer or at risk for
developing cancer comprises administering to the subject an agent that reduces cleavage
of a cell surface receptor interchain binding region from the cell. .
.
. . .
comprises determining an amount of cleavage
of a cell surface receptor interchain binding region from a cell surface, and evaluating
indication of cancer or potential for cancer based
upon the determining step.
. . .
determining a site of cleavage of a
cell surface receptor in a sample from a subject, and evaluating an indication of cancer or
potential for cancer based upon the determining step.

Another method of the invention involves treating a subject to reduce the risk of

or progression of cancer. The method comprises administering to a subject, who is known to be at risk for cancer or is diagnosed with cancer, an agent for inhibiting interaction of an activating ligand with a portion of a cell surface receptor that interacts with the activating. . .

Another method of the invention involves treating a subject to reduce the risk of or progression of cancer. The method comprises administering to a subject, who is known to be at risk of cancer or is diagnosed with cancer, an agent for preventing clustering of portions of cell surface receptors that interact with an activating ligand such as a growth factor. . .

Another method involves diagnosing a physiological state indicative of cancer or potential for cancer. The method comprises determining a specific cleavage site of MUC I distinguishable from a different cleavage state of MUC I.

Another method of the invention involves treating a subject having a cancer characterized by the aberrant expression of MUC 1 . comprising administering to the subject etomoxir in an amount effective to reduce tumor growth.

Another method of the invention involves treating a subject having a cancer characterized by the aberrant expression of MUC I, comprising administering to the subject L-cc-methyl-dopa in an amount effective to reduce tumor growth.

Another method of the invention for treating a subject having cancer characterized by the aberrant expression of MUC I, comprises administering to the subject calcimycin in an amount effective to reduce tumor growth.

Another method for treating a subject having a cancer characterized by the aberrant expression of MUC 1, comprises administering to the subject butylindazole in an amount effective to reduce tumor growth.

. . .

imply a disease-related cleavage site on the MUCI receptor;

Fig. 4 is a graph of percent cell proliferation that shows that an antibody against an epitope of the MUC I receptor which is proximal to the cell surface, and that dimerizes the receptor, enhances cell proliferation in a manner typical of a growth factor/receptor - antibody interaction;

Fig. 5 is a graph of percent cell proliferation that shows that an antibody against an epitope of the MUC I receptor which is proximal to the cell surface, and that dimerizes

the receptor, dramatically enhances. . . used to detect inhibitors of the MUC 1 -Ligand
interaction;
Fig. 13 shows a histogram illustrating the selective inhibition of proliferation of tumor
cells that aberrantly express the WC I receptor, in response to treatment with
compounds of the invention, and lack of an effect. . . of the WC I receptor and a multimerizing ligand(s);
Fig. 15 shows a histogram illustrating the selective inhibition of proliferation of tumor
cells that aberrantly express the WC I receptor, in response to treatment with drugs that
specifically inhibit MUCl positive cells;
Fig. 16 shows. . . to treatment with drugs that non-specifically inhibit cell proliferation;
Fig. 17 shows a histogram illustrating that drugs that selectivly inhibit proliferation of
tumor cells that aberrantly express the WC I receptor bind to the PSMGFR, while drugs
that non-selectively inhibit cell proliferation do not;
Fig. 18 is a graph showing that the inhibition of WC 1 -dependent cell proliferation
induced by an anti-tumor drug identified in accordance with the invention, is modulated
when a synthetic peptide, corresponding to the portion of MUC I that. .
.
. . .
a mechanism in which this portion is made
accessible to the ligand upon MUC I cleavage at a site associated with tumorigenesis that
causes release of the IBR from the cell.
. . .
shed, or cleaved. The cleaved IBR of interest is a
disease-associated cleavage, i.e. that type of cleavage that can result in cancer.
. . .
ratio with the IBR and forms part of the portion of MUC I that is shed upon cleavage in healthy and tumorigenesic cells.
. . .
type of interaction that occurs
between pairs of molecules including proteins, nucleic acids, glycoproteins,
carbohydrates, hormones and the like. Specific examples include antibody/antigen,
antibody/hapten, enzyme/substrate, enzyme/inhibitor, enzyme/cofactor, binding
protein/substrate, carrier protein/substrate, lectin/carbohydrate, receptor/hormone,
receptor/effector, complementary strands of nucleic acid, protein/nucleic acid
repressor/inducer, ligand/cell surface receptor, virus/ligand, etc.
. . .
the host system includes a synthetic species such as a polymer, dendrimer,
etc., or a naturally-occurring species, for example an IgM antibody, which is not simply
naturally present in the host system but is added to the host system from a source
external to. . .
. . .
a dimer, a
tetramer, a higher multimer, or a complex comprising a plurality of molecular species. In

the context of MUC I tumor cells, an activating ligand can be a species produced by the cells that interacts with the MGFRs on the surface of the WC 1 tumor cells in a manner that effects inductive multimerization.

A MUC I presenting cell refers to both non-cancerous and cancerous cells expressing MUC I and/or MGFRs on the surface. A WC I tumor cell or NWC 1 cancer cell or cancerous MUC1 cell refers to a cancerous tumor cell that aberrantly expresses MUC I and/or MGFR on its surface.

. . .
limited to, a binding species such as a peptide synthesized on a polystyrene bead, a binding species specifically biologically coupled to an antibody which is bound to a protein such as protein A, which is attached to a bead, a binding species that forms. .
.
. . .
cover in this coritext, means that there is no portion of the surface or 3o region that directly contacts a protein, antibody, or other species that prevents complete, direct coverage with the SAM. Le. in preferred embodiments the surface or region includes, across its. . .

The term cancer, as used herein, may include but is not limited to: biliary tract cancer; bladder cancer; brain cancer including glioblastornas and medulloblastomas; breast cancer; cervical cancer; choriocarcinoma; colon cancer; endometrial cancer; esophageal cancer; gastric cancer; hernatological neoplasms including acute lymphocytic and myelogenous leukemia; multiple myelorna; AIDS-associated leukemias and adult T-cell leukemia lymphoma; intraepithelial neoplasms including Bowen's disease and Paget's disease; liver cancer; lung cancer; lymphomas including Hodgkin's disease and lymphocytic lymphomas; neuroblastornas; oral cancer including squarnous cell carcinoma; ovarian cancer including those arising from epithelial cells, strornal. cells, germ cells and mesenchyrnal cells; pancreatic cancer; prostate cancer; rectal cancer; sarcomas including leiornyosarcorna, rhabdornyosarcoma, liposarcoma, fibrosarcoma, and osteosarcoma; skin cancer including melanoma, Kaposi's sarcoma, basocellular cancer, and squarnous cell cancer; testicular cancer including germinal tumors such as serninorna, non-serninorna (teratornas, choriocarcinomas), stromal tumors, and germ cell tumors; thyroid cancer including thyroid adenocarcinoma and medullar carcinoma; and renal cancer including adenocarcinorna and Wilms tumor . Preferred cancers are; breast, prostate, lung, ovarian, colorectal, and brain cancer
.

The term cancer treatment as described herein, may include but is not limited to: chemotherapy, radiotherapy, adjuvant therapy, or any combination of the aforementioned methods.. . .

Another treatment for cancer is surgery, which can be utilized either alone or in combination with any of the aforementioned treatment methods. One of ordinary. . .

An agent for prevention of cancer or tumorigenesis means any agent that counteracts any process associated with cancer or turnorigenesis described herein. For example, an agent that interacts with (e.g, binds to) to MGFR thereby reducing or preventing interaction, with. . .

. . .

in a cell-free assay containing the enzyme and WC I receptors, and the the rate or position of cleavage measured by antibody probing, Polymerase Chain Reaction (PCR), or the like. Alternatively, without first identifying enzymes that affect WC 1, agents are screened against cells. . . present WC 1, the supernatant removed, and the cell remain tested for accessibility of the MGFR portion, e.g. using a labeled antibody to the MGFR. Agents can be identified from commercially available sources such as molecular libraries, or rationally designed based on known agents. . .

. . .

reduces cleavage of the WC I receptor at any location. Such an agent can be used to treat a subject having cancer or at risk for developing cancer because if cleavage is prevented, then the accessibility of the MGFR, a functional receptor associated with cancer, is reduced or prevented. Such agents can be selected by exposing cells to a candidate agent and determine, in the supernatant,. . .

. . .

A subject, as used herein, refers to any mammal (preferably, a human), and preferably a mammal that may be susceptible to tumorigenesis or cancer associated with the abherrant expression of MUC I. Examples include a human, non-human primate, cow, horse, pig, sheep, goat, dog, or cat.. . .

The present invention involves, generally, novel molecular targets for drug screening, therapeutics and diagnostics related to cancers that are characterized by the aberrant expression of a class of cell surface receptors characterized by interchain binding regions. One such set of cancers are those characterized by the aberrant 3 o expression of MUC I. Much of the description of the invention herein involves. . . to identify other cell surface receptors that function by this or a similar mechanism, and to apply the invention to those cancers characterized by aberrant expression of receptors. The invention is based on a novel mechanism involving cell surface receptors that have regions that. . .

. . .
and progressing away from the cell. In
at least one U.S. provisional patent application (earlier
application(s)) filed by the
same inventors, entitled Tumor Markers and Drug Screening for
Tumorogenesis
Inhibition, relating to MUC I diagnostics and other techniques, at least
one region of
MUC I was defined differently. It is to. . .

Cleavage of MUCl may occur at a site at or near the C-terminal boundary
of the
IBR in tumor or cancer cells (between the cell and
the IBR), releasing the IBR from the
cell. Altematively,cleavageofWClmayoccurwithintheIBRitselftocause
sufficient disrupting of the IBRs such that the. . .
. . .
from intreacting with the MGFR portion of the
receptor, which is proximal to the cell relative to the IBR. In a
cancerous or tumor cell,
this reticulum may be lost, allowing ligand interaction with the MGFR.
. . .
proliferation; and (b) blocking the interaction
of this portion of the WC I receptor (MGFR) with its ligand(s), blocks
cell
proliferation. When tumor cell lines, in which the WC I
receptor is homogeneously
expressed across the entire cell surface, are treated with an IgG
antibody raised against
the MGFR portion of the WC I receptor, the rate of cell proliferation is
greatly
enhanced, see Fig. 5. Since IgG antibodies are bivalent, i.e.
one antibody simultaneously
binds to two adjacent MGFR portions on the cell surface, these results
demonstrate that
the antibody acts as an activating ligand, mimicing the effect
of a growth factor, which
dimerizes MGFR portions, and thus triggers a cell. . . of the
receptor with a
monomeric composition, thus preventing inductive multimerization and
subsequent
signaling cascades. For example, a single chain, or monovalent,
antibody raised against
the MGFR portion of the MUCl receptor would function as an effective
anti-cancer
therapeutic. Another therapeutic strategy is to block the activity of
enzymes that modify
the receptor, which may be required for some ligand. . .
. . .
histidine tag of the peptide, the beads were then incubated with
lysates and supernatants from a variety of cell types, including
cancer cell lines that
overexpress MUCL Enzyme inhibitors such as PMSF were added to some of
the lysates
and supernatants to circumvent problems. . .
. . .
containing some or all of these ligand
species. In one aspect, the invention involves modification and use of
the above species
as anti-cancer agents.
. . .
a protein known as Metastasis Inhibition Factor NM23,
which has been implicated in both the promotion and inhibition of
metastasis of human

cancers. Whether the role of NM23 is a tumor supressor or promoter may depend on the type of cancer. In ovarian, colon and neuroblastoma tumors, NM23 overexpression has been linked to a more malignant phenotype (Schneider J, Romero H, Ruiz R, Centeno MM, Rodriguez-Escudero FJ, NM23 expression in advanced and borderline ovarian carcinoma, Anticancer Res, 1996; 16(3A): II 97-202). However, breast cancer studies indicate that reduced expression of NM23 correlates with poor prognosis (Mao H, Liu H, Fu X, Fang Z, Abrams J, Worsham MJ, Loss of NM23 expression predicts distal metastases and poorer survival for breast cancer, Int J Oncol 2001 Mar; 1 8(3):587-91).

. . .

NOT added to lysate) corresponded to more than one protein species, including 14 3, which is a signaling protein implicated in many cancers, and cathepsin D, which is a protease and is also implicated in tumor progression. 14 3 exists as a dirner and can simultaneously bind to two, identical phospho-serine peptides. This protein has been shown to. . .

. . .

a high degree of homology to beta-lipotropin (Odell W, Wolfsen A, Bachelot 1, and Hirose F, (1979) Ectopic production of lipotropin by cancer The American Journal ofMedicine 66; pgs.

. . .

the position of enzyme cleavage is associated with receptor clustering, accessibility of adjacent portions of the receptor to putative ligands, and thus cancer. Agents that modulate the activity of this enzyme may be potent anti-cancer agents. Additionally, an early diagnostic test for cancers that aberrantly express MUC 1 may be based on detecting the portion of MUC I that self-aggregates (113R) circulating in bodily. . . cell surface after the release of the portion that self-aggregates (IBR - some or all of the PSIBR sequence) may be potent anti-cancer drugs. In addition, agents that block binding of the natural ligand to the remaining portion after the release of the IBR,. . . biomolecules and to artificially cluster the MGFRs. Another alternative agent, which can be used to artificially cluster the MGFRs is an IgM antibody raised against the MGFR or PSMGFR. This artifically-induced clustering may serve to keep the cytoplasmic tails clustered to prevent interaction with intracellular. . .

One aspect of the invention involves s novel drug screening assays, that identify therapeutics that interfere with the proliferation of tumor cells that aberrantly express MUC L The drug screen makes use of the new molecular target for cancer that is

disclosed herein. Another aspect of the invention involves therapeutics identified by the
drug screen. Yet another aspect of the invention involves methods for diagnosing
MUC I+ cancers, which is based upon the mechanism elucidated
by the inventors.

. . .
assay which can
rapidly identify agents that interrupt the interaction between the MGFR and its ligand(s)
and thus can be used as cancer therapeutics, (see Example 5a
and Fig. 12 for details).

60/317,302 and 60/317,314, both filed on September 5, 2001 and entitled COMPOSITIONS AND METHODS OF TREATMENT OF CANCER.

Agents so identified may be potent anti-cancer agents either
in monomeric form
or as polymers or dendrimers. Drug libraries and peptide libraries can be screened for
molecules that inhibit. . .

. . .
its ligands. These methods include but are not limited to phage display methods, yeast two-hybrid system, sandwich assays, surface plasmon resonance-based
assays, antibody-based assays, peptide bead assays for testing
with drug libraries, bead
assays, GFP-reporter assays, and the like. Ligands to the MGFR portion.
. .

. . .
used to block binding of the remaining extracellular portion of cleaved MUC I to its natural ligand, and can potentially inhibit cancer
growth.

. . .
of the invention is a drug screening assay for identification of drugs that can be useful for prevention and/or treatment of
cancer by altering the
cleavage state of WC 1 receptors on cells. In such assays, described in more detail
below, cultured cells are. . . and/or dosage or other conditions involving exposure to the drugs. These cells can be derived from a particular patient, or
can be tumor-associated or non-tumor-associated cell
lines. Customized therapeutic
protocols can be determined for a particular patient in this manner. The invention
involves, in one aspect, treating. . . below,
shown to affect the cleavage state of WC I of the patient's cells in a manner that
prevents, inhibits, or reverses cancer.

. . .
suspected that the incorrect cleavage of WC 1 on the surface of the cell causes the cascade leading to proliferation and
tumorigenesis, it would be
advantageous to test candidate drugs in a whole cell assay for their ability to affect
enzyme cleavage or the. . .

Colloids bearing an antibody, natural ligand, or small
molecule that binds to either the
cleaved portion of WC I, or the remaining extracellular portion (plus.
. .

. . .
contained within the shed fragment. The aggregation

potential of peptides released into the cell media is tested by adding colloids bearing an
antibody to a sequence distal from the self-aggregating portion, but not a repeat
sequence. In this way, antibody-presenting colloids would attach to upstream regions of
MUCL If the self-aggregating region was also attached to the released fragment, then
this would. . .

. . .
of these portions or other
structural constraint that inhibits their association with factors that promote cell
proliferation. Alternatively, IgM-type monoclonal or polyclonal antibodies raised
against the MGFR or PSMGFR could be utilizied. Each anti-MGFR IgM antibody could
be able to aggregate ten MGFRs on the cell surface to form preventative clusters.

. . .
I receptor can similarly be modified with other therapeutic agents. In this way,
such a therapeutic can be directed to the tumor cells. For example, an agent that binds to
the MGFR region of the WC 1 receptor can be modified with a radioactive substance to
destroy tumor cells that aberrantly express the WC I receptor. Other toxic substances,
such as ricin, as well as other therapeutics, can be. . . that bind to the MGFR could be modified
to present a imaging agent for use in diagnostic imaging of MUC 1+ tumors and
metastases. Such ligands can also, alternatively, be modified to act as drugs that can be
useful for prevention and/or treatment of cancer. In one embodiment, a ligand, which in
its unmodified form binds to multiple MGFRs causing inductive multimerization, is
modified to remove or. . .

The discoveries presented herein: (1) that the IBR of MUC I self-aggregates; (2)
that an antibody that dimerizes adjacent MGFR portions of the MUC I receptor leads to
proliferation of WC I presenting tumor cells; and (3) that proliferation of MUC I
presenting tumor cells can be inhibited by treatment with agents that target the MGFR
and block the MGFR against interaction with a ligand,. . . the cell that WC I remains clustered, and the MGFR is inaccessible to ligands such
as growth factors, and in a tumor cell, MUC I cleavage occurs such that enough of the
IBR is cleaved from the cell such that WC I does. . .

The above-mentioned mechanistic model predicts that in a subject with a WC I -
dependent tumor or who is prone to developing such a tumor, the portion of the MUC I
receptor that is shed will contain the IBR region of the receptor, leaving the MGFR
portion. . .

The cleavage state will differ between a healthy cell and a cell with

tumor potential. The
cleavage state determination can involve determining whether cleavage occurs in a
manner such that the normal interaction between the IBRs. . .
. . .
and/or a signaling entity. Generally, an assay as
described in WO 00/43791 or WO 00/34783 can be used. In a specific example,
antibodies to a portion of MUC I that would remain fastened to the IBR if the IBR is
cleaved from the cell, such as antibodies to the repeats
domain, are fastened to colloids.

The discovery that tumor cells can be treated with an agent that binds to the
MGFR of MUC 1, or a ligand of MGFR, in a manner that inhibits cell proliferation leads
to the conclusion that, in a diseased cell (a cancerous cell or a cell with potential for
becoming cancerous), cleavage of MUC I occurs in a manner that allows MGFR to
interact with at least one ligand in a manner that promotes turnorigenesis or cancer.
. . .
separated from the cell. The amounts of various receptor regions may be determined with any type of binding assay, e.g. an antibody-binding assay. For
example, antibodies that specifically bind to the constant region or the repeats may be
attached to surfaces (e.g. magnetic beads) to preconcentrate shed MUC I receptors prior
to determining levels of IBR present. Then, for example, after pre-concentration of
circulating MUC I receptors, antibodies to the IBR and antibodies to the constant region
can be allowed to bind to the cleaved receptors, and determination of the ratio of binding
of these antibodies reveals the ratio of IBR present relative to constant region present in
the cleaved receptors, which in turn reveals the amount. . . IBR relative to constant region present) for
detecting IBR at a cell surface is an indicator of the presence of a tumor or the potential
for the development of a tumor. A ratio that approaches 1: I when detecting these
regions in shed receptors is likewise an indicator of cancer potential. This determination
can indicate potential for tumor formation, existence of a tumor, progression of
tumorigenesis, etc., and can thereby serve as a diagnostic and/or a evaluator of treatment
for tuniorigenesis
Another diagnostic aspect of the invention involves. . . assay or a colloid bead assay (See above
discussion and Examples, below). Alternative techniques involve determining the
presence of the IBR using antibody probing assays, hybridization, PCR Reverse
Transcriptase PCR (rtPCR), Ligase Chain Reaction (LCR), cycling probe technology,
etc. In a preferred embodiment of the. . .

The determination, in a blood sample, of the amount of cleaved receptor carrying

IBR, either involving antibody binding ratios, colloid binding assays, or the like can be made on a bodily fluid sample, such as a blood sample and optionally compared with other samples (e.g. to monitor the subject's progression of tumorigenesis or progression for treatment of the same) and/or controls.

. . .

site can be studied without removal of the tissue from the subject). In either of these studies, a primary indicator of tumorigenesis or potential for tumorigenesis is the amount of MGFR at a cell surface accessible to interaction with external agents such as growth factors, etc. This determination can be made, for example, by determining the amount of an antibody to the MGFR region that binds to the sample, either using standard antibody binding study techniques, or by exposing the sample to colloids to which antibodies specific to the MGFR region have 3o been immobilized and determining binding of the colloids to the samples using techniques described in International patent publication numbers WO 00/34783 and WO 00/43791, referenced above. In another technique (perhaps more suited for an excised sample), antibodies to the MGFR region and to the IBR can be exposed to the sample and a determination made of the ratio of binding of each to the sample. A healthy sample will exhibit little or no antibody binding to the MGFR region. A sample indicating turnerigenesis or potential for tumorigenesis will show a non-zero ratio of MGFR antibody binding to IBR antibody binding.

. . .

a cell surface (rather than the amount of IBR in a shed portion) in a sample from a subject to evaluate cancer, or the potential to develop cancer in a subject.

. . .

information as to whether the IBR remains on the cell surface, or was shed from the cell surface, giving indication of cancer or turnorigenesis or the potential for either, as discussed above. Determining the site of cleavage can be accomplished by using enzyme-amplification methods. .

.

. . .

pre- and post-treatment levels of cleaved cell surface receptor IBR, or cell surface receptor IBR at the surface of a cell, in cancer cells or tissues may be used to diagnose cancer in a subject or assess the effectiveness of treatment in a cancer patient. In a preferred embodiment the cell surface receptor is MUC 1.

Comparison of the levels of the above-mentioned regions with levels from subjects known to be free of cancer may allow determination of the presence of cancer in the subject. An example, although not intended to be limiting, is that a determination of the presence of elevated levels of. . . in a sample from a subject,

when compared to a level determined in samples from control subjects, may suggest the
presence of cancer in the subject with elevated levels. Such methods of comparing levels
of cancer-associated markers between a sample from a subject and a control sample for
diagnostic purposes would be understood by one of ordinary. . .

Examples of such methods include Western blotting, ELISA, antibody precipitation,
PCR, LCR, rtPCR, cycling probe technology, and colloidal assays as described in
international patent application serial no. PCT/USOO/01997, filed 01/25/00, entitled
5Rapid. . .

. . .
aspect of the invention, the cleavage state of MUC I can be used to determine progression or regression of a subject's cancer over time. The cleavage state
also can be used to assess treatment parameters including, but not limited to: dosage,
method of administration,. . .

1 5 Another aspect of the invention involves extremely early-stage cancer diagnosis.

This aspect involves identification of patients who may be at risk for developing tumor
or cancer associated with abnormal cleaveage of MUC L These patients may not have
developed tumors, but may exhibit a cleavage state indicative of a condition that can lead
to cancer. In some instances, the subjects will already be undergoing treatment for
20 cancer, while in other instances the subjects will be without present cancer treatment. A
test for a genetic predisposition to cancers characterized by aberrant MUC 1 expression of
the invention is based on detecting genetic alterations in the MUC I cleavage enzyme(s),
over. . .

The fact that elevated levels of cleaved MUCl are found in the blood of cancer
patients is the basis for a blood test for breast cancer, which is not described herein.

. . .
is the identification of compounds that directly bind to the PSMGFR portion of the receptor. Therefore, a sensitive method for diagnosing
early tumors is to administer to the patient, compounds that bind to the PSMGFR region
that have also been derivatized with contrast or imaging agents. These compounds will
agglomerate onto tumors wherein this portion of the NWC I receptor is accessible.

. . .
one aspect of the invention is directed to methods for treating a subject diagnosed with or at risk of developing a cancer or tumor characterized
by the aberrant expression of MUCL The treatments of the present invention involve the
use of drugs or agents as described herein. That is, one aspect involves a series of

compositions useful for treatment of cancer or tumor characterized by the aberrant expression of MUC I, including these compositions packaged in kits including instructions for use of the composition for. . . a description of use of the composition for participation in any biological or chemical mechanism disclosed herein that is associated with cancer or tumor. The kit also can include instructions for use of a combination of two or more compositions of some embodiments of the invention.. . . via another known route of drug delivery. These and other embodiments of the invention can also involve promotion of the treatment of cancer or tumor according to any of the techniques and compositions and combinations of compositions described herein.

. . .

even though the patients exhibit indication for treatment of one of the compositions of the invention for a condition different from cancer or tumor, including conditions that can be unrelated to cell proliferation or conditions that can accompany cell proliferation, cancer, or tumor. That is, if a composition of the invention is known for treatment of a different condition, some embodiments of the present invention also involve use of that composition for treatments that accompany cell proliferation, cancer, or tumor disease where indicated. These and other embodiments of the invention can include such treatment where the dosage, delivery technique or vehicle,. . . timing of administration, or other factor differs from the use of the composition for treatment of the condition different from cell proliferation, cancer, or tumor. In another set of embodiments, treatment of .cell proliferation, cancer, or tumor with compositions of the invention may occur under 5 conditions that are similar to or overlap the use of compositions of. . . the invention for treatment of a different condition, but the compositions of the invention are promoted for treatments that accompany cell proliferation, cancer, or tumor or includes instructions for treatments that accompany cell proliferation, cancer, or tumor as mentioned above. As used herein, promoted includes all methods of doing business including methods of education, hospital and other clinical instruction,. . . written, oral, and electronic communication of any form, associated with compositions of the invention in connection with treatments that accompany cell proliferation, cancer, or tumor. Instructions can and often do define a component of promotion, and typically involve written instructions on or associated with packaging of compositions. . .

Subjects for whom certain treatment methods of the invention (with specific compositions directed toward cell proliferation, cancer, or tumor) are not intended are those who are diagnosed with a condition which may already call for

treatment with the
specific composition. Accordingly, one aspect of the invention involves
treatment of cell
proliferation, cancer, or tumor with a specific
composition disclosed herein for that
purpose, not in combination with another agent where the other agent has
been taught
previously for use in treatment of cell proliferation, cancer,
or tumor itself. Another
embodiment involves treatment of cell proliferation, cancer,
or tumor with this specific
composition alone, not in combination with any other active agent.
Another embodiment
involves treatment of cell proliferation, cancer, or
tumor with this specific composition
where the use of the composition in the treatment is specifically
instructed (through, e.g.

written instructions that can accompany the composition) for the
treatment of cell
proliferation, cancer, or tumor. In a preferred
embodiment of this aspect, the invention
involves treatment of cell proliferation, cancer, or
tumor with the specific composition
where the use of the composition in the treatment is specifically
instructed to affect a
mechanism associated with cell proliferation, cancer, or
tumor as disclosed herein.

. . .

treated with dru s useful according to
I 9
certain methods of the invention, including patients who are not
suffering from cell
proliferation, cancer, or tumor and who may or may
not be presently indicating
susceptibility to cell proliferation, cancer, or tumor
. In other words, the preventative
treatment preferably is directed to patient populations that otherwise
are free of disease
symptoms that call for. . .

. . .

NS 1 619 and etomoxir interrupt the interaction of
MGFR with its ligand(s) that otherwise would bind to MGFR and promote
tumorigensis.

In this aspect, the invention involves treatment of subjects associated
with tumor or
cancer associated with aberrant expression of MUC1 with these
agents or a combination.

. . .

interfering with the MGFR-ligand
interaction. All of the compounds inhibited cell proliferation, but
roughly half of the
compounds were toxic to both tumor cells that presented the
MUC I receptor as well as
cells that did not present this receptor. As discussed herein, the. .
.

. . .

to the MGFR
1 5 portion will have little or no toxic effects. Fusaric acid,
L-U.-methyl-dopa and etomoxir
selectively inhibited proliferation of tumor cel Is presenting
MUC I while leaving control
cells unaffected, see Fig. 13.

. . .
treatment with fusaric acid, but where the call for treatment with fasaric
acid did not specifically call for treatment directed toward tumors or cancers associated
with the abherrant expression of WC I, particularly in the dosages or other specific
protocols described previously in U.S. Patent No. 6,127,393. Specific diseases listed in
U.S. Patent No. 6,127,393 include skin cancer, breast cancer, prostate cancer, cervical
cancer, colon cancer, liver cancer and lung cancer. In one embodiment, the methods of
the present invention involve treatment with fusaric acid in dosages lower than that
described in U.S.. . .

. . .
to
the subject any one of calcimycin, fusaric acid, L-cc-methyl-dopa, butylindazone,
NS 1619 and etomoxir in an amount effective to lower the risk/prevent/reduce/inhibit
tumors or cancer associated with aberrant expression of MUC 1.

. . .
the specific route
of administration and like factors within the knowledge and expertise of the health
practitioner. For example, in connection with tumor or cancer associated with ablierrant
expression of NWC1, an effective amount is that amount which prevents interaction of
MGFR with its ligand that otherwise. . .

. . .
(for agents that act according to that mechanism) so as to slow or halt the development of or the progression of tumor or
cancer associated with aberrant expression of MUC 1. It is preferred generally that a
maximum dose be used, that is, the highest. . .

. . .
administer higher
and more frequent doses of the agent to a subject for example during or immediately
following a event associated with tumor or cancer, provided still that such doses achieve
the medically desirable result. On the other hand, it may be desirable to administer lower
2o. . .

As noted, different drugs act according to different mechanisms. Drugs according to one mechanism interfere with MGFR binding to a tumorigenesis-promoting
ligand, and do so to a particular degree relative to natural conditions for the subject in the
io absence of the drug.. . .

. . .
routes are available. The particular mode selected
will depend, of course, upon the particular combination of drugs selected, the severity of
the cancer condition being treated, the condition of the patient, and the dosage required
for therapeutic efficacy. The methods of this invention, generally. .
.

. . .
Parenteral routes include subcutaneous, intravenous, intramuscular, or infusion. Direct
injection may be preferred for local delivery to the site of the cancer. Oral administration
may be preferred for prophylactic treatment e.g., in a subject at risk of developing a
cancer, because of the convenience to the patient as well as the dosing schedule.
. . .
(e.g. tissue), such as (e.g. the vascular
cell wall), by coupling the liposome to a specific ligand such as a monoclonal antibody,
sugar, glycolipid, or protein.

Use of a long-term sustained release implant may be particularly suitable for
treatment of established cancer conditions as well as subjects at risk of developing a
cancer. Long-term release, as used herein, means that the implant is constructed and
arranged to deliver therapeutic levels of the active ingredient for at least 7 days, and
preferably 30-60 days. The implant may be positioned at the site of the tumor.

The therapeutic agent may be administered in alone or in combination with an
anti-cancer drug. If the therapeutic agent is administered in combination the compounds
may be administered by the same method, e.g. intravenous, oral, etc. or may be
administered separately by different modes, e.g. therapeutic agent administered orally,
anti-cancer drug administered intravenously, etc. In one embodiment of the invention
the therapeutic agent and the anti-cancer drug are co-administered intravenously. In
another embodiment the therapeutic agent and the anti-cancer drug are administered
separately.

Anti-cancer drugs that can be co-administered with the compounds of the
invention include, but are not limited to Acivicin; Aclarubicin; Acodazole
Hydrochloride; Acronine;. . .

HHHHHHGFLGLSNIKFRPGSVVVQLTLAFRE (SEQ ID NO: 4)
Histidine-Tagged Repeat Motif 2 (His-RM2).

GFLGLSNIKFRPGSVVVQLTLAFRE (SEQ ID NO: 8)
Repeat Motif 2 (RM2).

Histidine-tagged peptides were synthesized with the sequences shown in table 1
(the various regions of MUC 1). The lyophilized peptides were. . . 2. Row A contains the
His-PSIBR (primary sequence interchain binding region) peptide; Row B contains the
His-TR peptide; Row C contains the His-RM2 peptide; Row D contains the His-
PSMGFR peptide. Column 1 contains the His-PSIBR peptide; Column 2 contains the

His-TR peptide; Column 3 contains the His-RM2 peptide; and Colurrm 4 contains the His-PSMGFR peptide. The solutions were observed for a color change. A change in solution color from. . . sequence of the interchain binding region (PSIBR), self-aggregates in a high affinity interaction, suggesting a mechanism by which the MUCl receptor confers tumorigenesis.

Example lb: Relationship Between MUCI Cleavage Site in Tumor Conditions and NWC I Interchain Bindi

This example investigates the ability of peptide sequences near the boundary between the MGFR and P SIBR. . . the MUC 1 receptor to participate in self-aggregation, and thereby elucidates a probable cleavage site of NWC I that is associated with tumorigenesis or cancer.

This strongly suggests that cleavage of the MUC I receptor in tumors or cancers associated with aberrant expression of MUC I occurs at or near the boundary between the PSMGFR and PSIBR sequences, since it is demonstrated herein that in tumor cells that overexpress MUC I, the MGFR is accessible by agents that reduce cell proliferation by inhibiting the interaction between MGFR and. . . otherwise would promote cell proliferation. This also strongly suggests that the IBR is shed in cleavage of MUC I receptor in tumor or cancer associated with aberrant expression of WC I, but is not shed in cleavage of MUC I when WC I is normally expressed. . . That is, that the cleavage site of MUC I is at or near the C-terminal boundary of the IBR in tumor or cancer cells and IBR at or near the N-terminal boundary of the IBR in healthy cells.

In the remaining examples, the mechanism described above for cancer associated with aberrant expression of MUC I, in which an activating ligand (which is a growth factor) binds to multiple MGFRs at. . . which causes proliferation (inductive multimerization), is confirmed. Briefly, the mechanism is confirmed by showing that exposure of cells to a bivalent antibody raised 2o against MGFR induces cell proliferation characterized by a growth/response curve typical of a growth factor/receptor - antibody response (Example 2, below); the activating ligand produced by MUC I -presenting cells binds multiple PSMGFRs, and the amount of activating ligand. . . each cell type is proportional to the amount of MUC I receptor produced by that cell type (Example 3a-b, below); MUCl tumor cells produce a species that is a multimer (Example 4b, below); and drugs found to be specific for MUC I tumor cells (drugs that inhibit proliferation in MUC 1 tumor cells but not other cells) are shown to bind to MGFR at cells, while those that are not

specific (those that
inhibit MUC I tumor cells and other cells) are toxic in that
they bind to the multimeric
ligand and thereby remove it from interaction with. . .
. . .
of the MGFR portion of the WC I receptor triggers enhanced
Cell Proliferation Consistent with the Mechanism Presented for MUC I
Tumor Cells
This example demonstrates the effect of dimerization on the MUC I
receptor. In
this example it is shown that exposure of cells to a bivalent
antibody grown against the
MGFR region of the MUC I receptor, at varying concentration, results in
enhanced cell
proliferation (or lack thereof) consistent with the mechanism presented
for MUC1 tumor
cells. A bivalent antibody was raised against PSMGFR (i.e., a
single antibody having
the ability to bind simultaneously to two MGFRs was produced). MUC I
tumor cells
(T47Ds) were exposed to this antibody, and cell proliferation
was studied as a ftinction
of concentration of the antibody. A growth/response curve
typical of a growth
factor/receptor - antibody response was observed.
Specifically, at concentration low
enough that only a small portion of the cells were exposed to the
antibody, cell -
proliferation was low. At a concentration of antibody high
enough that one antibody
could bind adjacent MGFRs, cell proliferation was maximized. At a high
excess of
antibody, each antibody bound only a single MGFR,
rather than dimerizing adjacent
MGFRs, and proliferation was reduced.

T47D (HTB- 1 3 3) cells, a human breast cancer cell line that
overexpresses
MUC I, were cultured to 30% confluency. An antibody raised
against the PSMGFR
portion of the WC I receptor, i.e. an antibody to the MFGR
(Zymed, San Francisco,
California, USA), was added to cells at varying concentrations in a
multi-well cell
culture plate. As a negative control, a second set of T47D cells was
treated with an
irrelevant antibody (anti-streptavidin). Prior to adding
antibody, cells were counted (at
time zero). All experiments were performed in triplicate. Cells were
allowed to grow in
a C02 incubator under. . . well) at 24 hours and again at 48 hours.
Results, see Fig. 4, show that in a
concentration-dependent manner, addition of antibody caused
enhanced cell proliferation
compared to the proliferation of the same cells treated with a control
antibody. Figure 4
is a graph in which measured cell growth at 24 and 48 hours is plotted
as a function of
anti-PSMGFR concentration. At the optimal antibody
concentration, when presumably
one antibody binds bivalently to two MGFR portions of the WC I
receptor, i.e.

In a similar experiment, a concentration of the anti-PSMGFR

antibody,
identified to maximize cell proliferation, was added to a first group of T47D tumor cells,
grown as described above. The same amount of the anti-PSMGFR antibody was added
to a set of control cells, K293 cells. Figure 5 shows that the addition of the anti-
PSMGFR antibody to MUC I tumor cells (T47D) enhanced proliferation by 180% 24
hours, but had no effect on the control cells. The growth of the T47D cells plateaued to
saturation, for cells with added antibody, at 48 hours. Control cells never reached
saturation within the time frame of the experiment and were at 70% confluency at. . .
. . .
Activating Ligand Produced by MUCI-Presenting Cells Binds Multiple PSMGFRs
In this example, it is demonstrated that the activating ligand that triggers MUC I
tumor cell proliferation binds multiple PSMGFRs
simultaneously. Colloid particles were produced that carry immobilized PSMGFRs, and suspensions of these colloids were
exposed to lysate and supernatants of (1) MUC1 tumor cells, or (2) control cells. MUC I
tumor cell lysates/supematants caused the colloids to aggregate (suspension turns blue)
because the activating ligand contained in them binds MGFRs on different. . .

Lysates and supernatants from four different tumor-associated cell lines (HTB- 1 3 3 (also
called T47D), CRL- 1 500, CRL 1504 and CRL- 1 902; ATTC, American Type. . .
. . .
Rows E-H contained colloid particles carrying a random sequence peptide. Columns 2, 5, 8, and I I contained lysates from a tumor cell line that
overexpresses NWC1 (HTB-133). Columns 3, 6, 9, and 12 contained lysates from a
tumor cell line that does not expresses WC 1 (CRL- 1 902). Columns 1, 4, 7, and 1 0
contain lysates from a tumor cell line that expresses, but does not overexpress, NWC I
(CRL- 1 504). Columns 1-3: NTA concentration on colloid: 20 micromolar;. . .
. . .
absence (Fig. IO) of the protease inhibitor PMSF
io (phenyl methyl sulfonyl fluoride). Lysates from T47D cells were used because this
breast tumor cell line was known to overexpress MUC I; additionally, the inventors
presented evidence herein (see Fig. 8A-D) that this cell line. . .
. . .
Culture Collection,
Manasses, VA) and are all breast carcinoma cell lines. Some lines have been shown to
express or over express the tumor marker receptor MUC 1, Her2/neu or the oncogenic
enzyme cathepsin K.
. . .
from Mediatech supplemented with I mM sodium
pyruvate, IO% FB S

Example 4b: Demonstration that the Ligand That Interacts with MUC 1 Cancer Cells
is a Multimer
In this example, it is demonstrated that a ligand produced by MUCl cancer cells
that triggers cell proliferation in these cells is a multimer.
. . .
known as Metastasis Inhibition Factor NM23,
which has been implicated in both the promotion and inhibition of metastasis of human
1 5 cancers. Whether the role of NM23 is a tumor
supressor or promoter may depend on the
type of cancer. In ovarian, colon and neuroblastorna
tumors, NM23 overexpression has
been linked to a more malignant phenotype (Schneider J, Romero H, Ruiz R, Centeno
MM, Rodriguez-Escudero FJ, NM23 expression in advanced and borderline ovarian
carcinoma, Anticancer Res, 1996; 16(3A): II 97-202). However, breast cancer studies
indicate that reduced expression of NM23 correlates with poor prognosis (Mao H, Liu H,
Fu X, Fang Z, Abrams J, Worsham MJ, Loss of mn23 expression predicts distal
metastases and poorer survival for breast cancer, Int J Oncol
2001 Mar; 1 8(3):5 87-9 1).
. . .
from the protein gel band described in Figures
9 and IO and that are derived from a protein implicated in many cancers called
Metastasis Inhibition Factor NM23 are shown below in Table 4. NM23 exists as a
hexamer and may recognize an unmodified form. . .
. . .
NOT
added to lysate) corresponded to more than one protein species, including 14 3, which
is a signaling protein implicated in many cancers, and
cathepsin D, which is a protease
and is also implicated in tumor progression. 14 3 exists as a dimer and can
simultaneously bind to two, identical phospho-serine peptides. This would dimerize the
MGFR portion. . .
. . .
QPGITFIAAK
3) human annexin V with Proline substitution by Thrionine gi: 3212603
GLGTDEESILTLLTSR
DLLDDLKSELTGK
SEIDLFNIR
Examples 5a-d: Drug Studies Consistent with Mechanism Presented for MUC1 Cancer
In these examples, drugs that inhibit proliferation in MUC I tumor cells
specifically were compared to drugs that inhibit proliferation in both MUC1 tumor cells
2o and other cells. Drugs, both specific and non-specific, were identified by exposing them
to PSMGFR-presenting colloids in the presence of WC 1 tumor cell lysates. Drugs
were identified as those that prevented colloid-colloid interactions. Cell studies resulted
in a separation of these drugs into two groups - a group specific for MUC I tumor cells

and a non-specific group. Non-specific drugs did not bind to PSMGFR, but are
presumed to bind the activating ligand, and inhibit. . . somewhat toxic to both
cell types, since they remove the activating ligand from interaction with the cells. Drugs
specific for WC 1 tumor cells were found to bind to PSMGFR on beads, as
demonstrated by HPLC analysis of the product of cleavage of PSMGFR. .
.
. . .
of the MUC I Recepto
with its Activating Ligand(s)
The following is an example of a working drug screening assay to identify anti-
cancer agents. In this example, a histidine-tagged peptide derived from the portion of the
MUC I receptor that remains attached to the. . .

The data below demonstrates the ability of anti-tumor drugs identified in
accordance with the invention, specifically, calcimycin, fusaric acid, L-(X-methyl-dopa,
butylindazone, NS 1 619 and etomoxir to inhibit proliferation of. . .
. . .
the interaction of the MGFR portion of the receptor with its activating ligands will
block the proliferation of MUC I -presenting tumor cells. Therefore, drugs that were
I 0 identified using the in vitro drug screening assay described in Example 5a were tested. . .
. . .
compared. As seen in Fig. 13, Etomoxir, L-alpha-
methyl DOPA, and Fusaric acid selectively inhibited proliferation of the NWC I -
expressing tumor cells over K293 negative control cells. The DMSO control cells (both
T47D and K293) show that DMSO alone does not effect cell proliferation. Fig. 13 is a
histogram illustrating the selective inhibition of proliferation of tumor cells that
aberrantly express the MUC I receptor (T47D cell line), in response to treatment with
compounds of the invention, and lack. . .
. . .
that were shown in the ftinctional cell
proliferation assay (see Example 5b) to selectively inhibit the proliferation of WC I -
presenting tumor cells by either directly binding to the MGFR portion or by acting on its
modifying enzymes. Figure 15 is a bar graph that compares the percentage cell growth
of WC 1 tumor cells (T47Ds) to a control cell line (K293 s), in response to treatment
with novel drugs, (described in greater detail in. . .
. . .
provisional patent applications serial nos. 60/317,302 and 60/317,314, both filed on
September 5, 2001 and entitled COMPOSITIONS AND METHODS OF TREATMENT
OF CANCER). As is readily apparent, this group of drugs dramatically inhibited or
completely prevented the proliferation of WC I -presenting tumor cells, while leaving
the control cells, in most cases, unaffected.

. . .
provisional patent
applications serial nos. 60/317,302 and 60/317,314, both filed on
September 5, 2001 and
entitled COMPOSITIONS AND METHODS OF TREATMENT OF CANCER) on
cell
growth for WC I -presenting cells (T47D) and a control cell line (K293).
Notably, this
group of drugs, which presumably. . .
. . .
6: Modulation of Inhibitory Effect of Etomoxir on Cell Proliferation
Etomoxir, identified as a composition useful in treatment of NWC 1
-dependant
tumors in this invention, was shown to be specific for MGFR by
modulating its effect on
cell proliferation via competetive inhibition of. . .
. . .
Drugs That Affect MUC 1 Cleavage State
The release of the MUC I IBR can be correlated to the progression of
cancer.

Tumor derived cells expressing a cell surface receptor of the
type described
above, are cultured and treated with a drug candidate. Following. . .

Colloids bearing a binding peptide e.g. an antibody against a
constant region of the
receptor, remote from the enzyme cleavage site (amino acid 42 5 -479 for
MUC 1;
3o. . .
. . .
to the diagnostics and screening assays of the invention, the invention
relates to therapeutic methods for the treatment and prevention of
cancer and related
products. For instance, in one aspect the invention relates to a method
for treating a
subject having a cancer or at risk of developing
cancer by administering to the subject an
agent that reduces cleavage of a cell surface receptor IBR from a cell
surface receptor.

CLMEN 10 A method of treating a subject to reduce the risk of or progression
of cancer
comprising:
administering to a subject who is known to be at risk for cancer
or is diagnosed
with cancer an agent for inhibiting interaction of an
activating ligand with a portion of a
cell surface receptor that interacts with the. . .

16 The method of claim IO, wherein the cancers is selected
from the group
consisting of. breast, prostate, lung ovarian, colorectal, and
brain cancer.

31 A method of treating a subject to reduce the risk or of progression
of cancer
comprising:
administering to a subject who is known to be at risk of cancer
or is diagnosed
with cancer, an agent for preventative clustering of portions
of cell surface receptors
that,interact with an activating ligand such as a growth factor. . .

36 The method of claim 3 1, wherein the cancer is selected from the group consisting ofe breast, prostate, lung ovarian, colorectal, and brain cancer.

84 A peptide species as in claim 68, wherein the fragment comprises at least a fragment of the sequence that corresponds. . . I that interacts with an activating ligand such as a growth factor to promote cell proliferation in association with MUC I -dependent tumorigenesis.

. . . remains attached to the cell surface after shedding of the cell surface receptor interchain binding region in association with MUC I -dependent tumorigenesis such that a biornolecule that interacts with that portion of WC I that remains attached to the cell surface after shedding of the cell surface receptor interchain binding region in association with MUC I -dependent tumorigenesis interacts with the fragment.

. . . in claim 109, wherein the synthetic drug is a derivative of etomoxir.

113. A method for treating a subject having a cancer characterized by the aberrant expression of MUC1, comprising: administering to the subject ftisaric acid in an amount effective to reduce tumor growth.

114. A method as in claim 1 13, wherein the subject is otherwise free of symptoms calling for treatment with calcimycin.

115. A. . . levels of shed interchain binding region are reduced relative to a control sample.

119. A method for treating a subject having a cancer characterized by the aberrant expression of WC I, comprising: administering to the subject etomoxir in an amount effective to reduce tumor growth.

120. A method as in claim 119, wherein the subject is otherwise free of symptoms calling for treatment with etomoxin

121. A method. . . levels of shed interchain binding region are reduced relative to a control sample.

125. A method for treating a subject having a cancer characterized by the aberrant expression of MUC I, comprising: administering to the subject L-(x-methyl-dopa in an amount effective to reduce 1 5 tumor growth.

126. A method as in claim 125, wherein the subject is otherwise free of symptoms calling for treatment with L-(x-methyl-dopa.

127. A. . . levels of shed interchain binding region are reduced relative to a control sample.

131. A method for treating a subject having a cancer characterized by the aberrant expression of WC 1, comprising: administering to the subject calcimycin in an amount effective to reduce tumor growth.

132. A method as in claim 13 1, wherein the subject is otherwise free of symptoms
calling for treatment with calcimycin.
133. A. . . levels of shed interchain binding region are
reduced relative to a control sample.
137. A method for treating a subject having a cancer
characterized by the aberrant
expression of WC I, comprising:
administering to the subject butylindazole in an amount effective to reduce tumor
growth.
138. A method as in claim 137, wherein the subject is otherwise free of symptoms
calling for treatment with butylindazole.
. A method. . . levels of shed interchain binding region are
reduced relative to a control sample.
143. A method for treating a subject having a cancer
characterized by the aberrant
expression of MUC 1, comprising:
administering to the subject NS 1 619 in an amount effective to reduce tumor
growth.
144. A method as in claim 143, wherein the subject is otherwise free of symptoms
calling for treatment with NS 1619.
145. A. . . composition and the biomolecule; and
determining disruption of the interaction by the candidate drug.
150. A method of treating a subject having cancer or at risk
for developing cancer
comprising:
administering to the subject an agent that reduces cleavage of a cell surface
receptor.
151. A method of treating a subject having cancer or at risk
for developing cancer
comprising:
administering to the subject an agent that reduces cleavage of a cell surface
receptor interchain binding region from the cell surface.
152. The. . . -
corresponds to amino acids 1085 through 1109 of Genbank accession # PI5941, PID
G547937).
156. The method of claim 150, wherein the cancer is selected
from the group
consisting of. breast, prostate, lung ovarian, colorectal, and
brain cancer.
157. The method of claim 150, wherein the cancer is
characterized by the aberrant
expression of the WC I receptor.
158. A method comprising:
determining an amount of cleavage of a cell surface receptor interchain binding
region from a cell surface; and
evaluating indication of cancer or potential for
cancer based upon the determining
step.
159. A method as in claim 158, wherein the cell surface receptor is MUCL
160. A method as in claim 158, comprising diagnosing cancer in
a subject by
determining an amount of shed cell surface receptor interchain binding region in a
subject sample; and
evaluating indication of cancer or potential for

cancer based upon the determining
step.
161. A method as in claim 158, wherein the evaluating step comprises correlating the
amount in a sample to an wriount in a control as an indication of cancer or potential for
cancer.
. A method as in claim 158, comprising:
determining an amount of cell surface receptor interchain binding region at the
surface of a cell from a subject; and
evaluating indication of cancer or potential for
cancer based upon the deten-nining
step.
163. The method of claim 158, wherein the interchain binding region comprises a
contiguous amino acid sequence of. . . 160, wherein the sample is a proliferating cell line derived
from a subject's cells.
. The method of claim 158, wherein the cancer is characterized by aberrant
expression of MUC I.
171. The method of claim 158, wherein the amount of interchain binding region is
determined. . . by a method selected from the group consisting of MALDI, western blotting,
PCR, LCR, rtPCR, cycling probe technology, gel electrophoresis, or antibody-based
assay, magnetic cell sorting, flourescence activated cell sorting, bead-based assays or an
ELISA assay.
172. The method of claim 158, wherein the amount. . . method comprising:
determining a site of cleavage of a cell surface receptor in a sample from a
subject; and
evaluating an indication of cancer or potential for
cancer based upon the
determining step.
176. The method of claim 175, wherein the cell surface receptor is MUC I.
177. The method of. . . blood.
180. The method of claim 175, wherein the sample is a tissue sample.
181. The method of claim 175, wherein the cancer is selected from the group
consisting of. breast, prostate, lung, ovarian, colorectal, and brain cancer.
182. A method as in claim 175, wherein the cancer is characterized by the aberrant
expression of WC I.
183. The method of claim 175, wherein the site of cleavage is determined. . . a
method selected from the group consisting of MALDI, western blotting, PCR, LCR,
1 5 rtPCR, cycling probe technology, gel electrophoresis, or antibody-based assay, magnetic
cell sorting, floureseence activated cell sorting, bead-based assays or an ELISA assay.
184. The method of claim 175, wherein the. . . of claim 185, wherein the surface cell receptor is WC I.
187. A method of diagnosing a physiological state indicative of cancer or potential for
cancer, comprising determining a specific cleavage state of WC I distinguishable from

a different cleavage state of WC1.
. A method comprising:
determining a. . . 188, comprising comparing the first amount to the second
amount as an indication of progression of and/or effectiveness of treatment for cancer.
190. A method as in claim 188, comprising comparing the first amount to the second
amount as an indication for administration of an agent for prevention of cancer.
191. A method as in claim 188, wherein the subject is undergoing treatment for
cancer, the method comprising
comparing the first amount to the second amount as an indication of effectiveness
of the treatment.
192. AmethodasinclaimI88,whereinthecellsurfacereceptorisWC1.
193. The method. . . method of claim 188, wherein the sample is a tissue sample.
I 0 199. The method of claim 188, wherein the cancer is selected from the group
consisting of. breast, prostate, lung, ovarian, colorectal, and brain cancer.
. . .
by a method selected from the group consisting of MALDI, western blotting,
PCR, LCR, rtPCR, cycling probe technology, gel electrophoresis, or antibody-based
assay, magnetic cell sorting, flourescence activated cell sorting, bead-based assays or an
ELISA assay.
202. The method of claim 188, wherein the amount. . .

=>

---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	14.60	23.28

STN INTERNATIONAL LOGOFF AT 14:43:49 ON 13 JUN 2006